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The Adolescent and Young Adult (AYA) Horizon Study: An AYA cancer survivorship cohort

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Abstract

Background: In the United States (U.S.), >45,000 adolescent and young adult (AYA) women are diagnosed with cancer annually. Reproductive issues are critically important to AYA cancer survivors, but insufficient information is available to address their concerns. The AYA Horizon Study was initiated to contribute high-quality, contemporary evidence on reproductive outcomes for female cancer survivors in the U.S.

Methods: The study cohort includes women diagnosed with lymphoma, breast, melanoma, thyroid, or gynecologic cancer (the 5 most common cancers among women ages 15–39 years) at three study sites: the state of North Carolina and the Kaiser Permanente health systems in Northern and Southern California. Detailed information on cancer treatment, fertility procedures, and pregnancy (e.g. miscarriage, livebirth) and birth (e.g. birth weight, gestational length) outcomes are leveraged from state cancer registries, health system databases and administrative insurance claims, national data on assisted reproductive technology procedures, vital records, and survey data.

Results: We identified a cohort of 11,072 female AYA cancer survivors that includes >1,200 African American women, >1,400 Asian women, >1,600 Medicaid enrollees, and >2,500 Hispanic women using existing data sources. Active response to the survey component was low overall (N=1,679), and notably lower among minority groups compared to non-Hispanic white women.

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Conflicts of Interest: The authors wish to disclose that Mr. Wantman is a partner at Redshift Technologies, Inc., the data vendor for the Society of Assisted Reproductive Technology. The authors declare there are no other potential conflicts of interest.

Conclusions: Passive data collection through linkage reduces participant burden and prevents systematic cohort attrition or potential selection biases that can occur with active participation requirements.

Impact: The AYA Horizon study will inform survivorship planning as fertility and parenthood gain increasing recognition as key aspects of high-quality cancer care.

Introduction

Five-year survival exceeds 80% for the >45,000 U.S. women diagnosed with an adolescent or young adult (AYA) cancer each year.[1] The AYA age range is defined by the National Cancer Institute as cancer diagnoses that occur at ages 15–39 years. This age range was selected, in part, due to the less favorable annual percent change in 5-year survival during 1975–1998 for 15–39 year-olds compared to their younger or older counterparts.[2] Additional rationale exists for defining the AYA age-range based on the unique concerns of AYAs who may be completing their education; establishing careers, relationships, and families; and developing personal, medical, and financial independence.[3]

For AYAs who may want to have children in the future, counseling on the potential impact of cancer treatment on fertility, and options for fertility preservation, is recognized as a critical component of high-quality cancer care.[4] Accepted, non-experimental fertility preservation strategies for women (embryo or oocyte cryopreservation) have historically required harvesting mature oocytes, and have therefore not been available to pre-pubertal childhood cancer survivors.[5] In 2019, the experimental designation was lifted from ovarian tissue cryopreservation, which will increase options for pre-pubertal females in the future.[6] Risk factors for infertility after cancer treatment among AYA women include alkylating agent-based chemotherapy, cranial radiation (due to disruption of hypothalamic-pituitary regulation), pelvic radiation (due to ovarian/uterine exposure), or gynecologic surgery.[7] Other late effects, such as cardiovascular or pulmonary impairments from radiation or anthracycline chemotherapies, may also adversely impact fertility or pregnancy outcomes after cancer treatment through indirect effects on blood volume regulation.[4,8] Fertility risks are also related to a woman's age at the time of cancer treatment, and the duration and dose intensity of therapy.[7]

Even in the absence of toxic therapies, time spent in active cancer treatment can disrupt relationships or may cause women to postpone childbearing plans to older ages when fertility is lower and pregnancy carries greater risks. Additional, indirect, consequences of cancer diagnosis and treatment may also impact the likelihood of pregnancy or reproductive planning. Such consequences may include altered self-image, sexual dysfunction, financial strain, depression, anxiety, or fears of recurrence, passing on inherited or treatment-related health risks, or bereaving a child.[4,9]

Existing evidence for adverse birth outcomes among AYAs with cancer comes, in part, from registry-based studies in Canada, Europe, and Australia. Studies report 30–70% lower livebirth rates (RR=0.3–0.7) and 1.2 to 3.2-fold higher risks of preterm birth, low birth weight and cesarean delivery as compared to women without a cancer diagnosis, particularly among women with a history of breast cancer or lymphoma.[10–18] Prior linkage studies in

North Carolina[19] and other U.S. southeastern states[20] have also reported elevated risks of preterm birth and low birth weight after a cancer diagnosis, but were unable to consider detailed cancer treatment or fertility preservation information. Compared to naturally-conceived pregnancies and births, Assisted Reproductive Technology (ART) procedures are associated with a 20% increased risk of pregnancy loss[21] and 1.6–2.7-fold increase in adverse birth outcomes (in singleton pregnancies)[22] among infertile couples, and may be an important contributor to pregnancy risks among cancer survivors. Female cancer survivors may use ART procedures (embryo or oocyte cryopreservation) as fertility preservation strategies prior to cancer treatment, or initiate ART after cancer treatment for fertility concerns.

Racial and socioeconomic disparities in cancer treatment and health outcomes in the U.S. argue for a cautious approach in generalizing from AYA cancer studies conducted in other countries. U.S. healthcare is characterized by complex and variable systems and insurance policies, with patients responsible for high out-of-pocket costs. Currently, a minority of states (10/50) mandate coverage for iatrogenic infertility.[23] Egg or embryo freezing can have initial costs $10,000-$15,000, with storage costs of approximately $500 annually, and additional costs per cycle at the time of retrieval.[24] In the cancer context, fertility preservation services may be discounted by individual clinics or providers; and some financial assistance programs are offered through private foundations, cancer advocacy groups, or non-profit organizations.[25] However, cost is an undeniable barrier to the widespread and equitable implementation of fertility preservation strategies.

Research to address reproductive outcomes after cancer has been challenging to perform in the U.S. due in part its decentralized healthcare system, but such research is critical given the pronounced disparities in cancer care and reproductive outcomes in minority and low-income U.S. populations. Adverse birth outcomes are more common in the U.S. general population overall compared to Canada, Australia, and many European countries,[26–28] and especially among minority and low-income women. In the U.S., 10% of livebirths are preterm; and 14% of Black women deliver preterm compared to 9% of White women.[29] Birth risks to cancer survivors in minority and low-income populations may be further impacted by inequities in cancer care[30] and access to fertility preservation or other assisted reproductive technologies.[31]

National guidelines uniformly recommend fertility counseling for AYA patients before cancer treatment,[5,6] but most AYAs report needing more information on fertility and reproduction issues before and after cancer treatment.[32–34] The AYA Horizon Study was initiated to examine pregnancy outcomes after diagnosis of the most common AYA cancers in women. The cohort is embedded within U.S. populations that reflect contemporary cancer treatment strategies and childbearing patterns, and leverages existing data sources and passive follow-up methods to identify a representative and diverse cohort of AYA women with and without cancer.

Cohort infrastructure and methods

Study population

The AYA Horizon cohort includes women diagnosed with the five most common types of cancer in the AYA age group (breast, thyroid, melanoma, lymphoma, uterine, cervical, and ovarian cancers (latter three types grouped as gynecologic cancer))[9] in North Carolina (2000–2015) and Kaiser Permanente Northern California (KPNC) or Southern California (KPSC) health systems (2004–2016) at ages 15–39 years (Figure 1 and Table 1). The study was approved with waivers of informed consent by each Institutional Review Board (KPNC, KPSC, UNC) and complies with recognized ethical guidelines. Cancer diagnoses are identified from the statewide Central Cancer Registry in North Carolina and KPNC/KPSC's regional cancer registries. KPNC and KPSC are the two largest member sites of the NCI-funded Cancer Research Network, a consortium of research groups affiliated with non-profit integrated health care systems.[35–37] KPNC and KPSC cover about 9 million lives and are characterized by stable, long-term retention rates among enrollees, including those diagnosed with cancer.[38] The North Carolina Central Cancer Registry is a gold-certified member of the North American Association of Central Cancer Registries (NAACCR) within the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries. The KPNC and KPSC cancer registries also adhere to NAACCR standards and report to the NCI's Surveillance, Epidemiology, and End Results (SEER) cancer registries. The University of North Carolina (UNC) Cancer Information Population Health Resource (CIPHR) links North Carolina Central Cancer Registry data with public and private payer administrative insurance claims (available starting in 2003) to obtain detailed cancer treatment information.[39] Across all ages and cancer types, the CIPHR linkage covers 80% of all cancers diagnosed in the state through 2015 (up from about 70% of all cancers through 2010).[39]

Monthly enrollment was identified from membership files for the KP health systems, and from the public and private insurers that are included in the UNC CIPHR linkage. We required women to be enrolled at diagnosis with 6-months continuous enrollment prior to diagnosis (allowing 90-day gaps) in the KPNC and KPSC health systems and among the privately insured in North Carolina (Table 1). Medicaid enrollees in North Carolina were required to be enrolled within 1 month of diagnosis but were not required to have continuous enrollment prior to diagnosis, to account for the potential for cancer diagnosis to be a qualifying event for enrollment. Women in North Carolina were also required to have 6 months continuous enrollment (with no gaps) after diagnosis to ensure that the first six months of cancer treatments were fully captured. After applying the continuous enrollment criteria, 24% (N=3,085) of the AYA cancer cases in North Carolina diagnosed during 2003–2015 (N=13,064) remained in the CIPHR sample. The non-CIPHR AYA population in North Carolina had similar demographic and clinical characteristics compared to the CIPHR population with the exception being that the CIPHR population had a lower percentage of Hispanic ethnicity (3.0% vs. 7.7%)(Table 2).

Across study sites, cancer types were defined according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography and histology codes using the

AYA Site Recode ICD-O-3/WHO 2008 definitions.[40] Gynecologic cancers included cervical and uterine carcinomas, carcinomas of the gonads, and germ cell and trophoblastic neoplasms of the gonads, as defined in the AYA Recode. Cancer diagnoses are all invasive, except for breast cancer where *in situ* disease was also included as women may elect to have cancer treatments equivalent to early stage invasive disease (e.g. mastectomy, endocrine therapy).

Cancer treatment information

Use of specific chemotherapy agents, including alkylating agents (e.g. cyclophosphamide), anthracyclines, and biologic agents, were identified using EHR data at KPNC and KPSC [41] and cancer treatment insurance claims in North Carolina within 12 months of diagnosis.[39] Chemotherapy drug lists and procedure codes from the International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10), Healthcare Common Procedure Coding System (HCPCS), Common Procedural Terminology (CPT), and National Drug Codes (NDCs) were used to identify cancer treatments in the claims data. Treatment types were defined using lists from the Cancer Research Network published on the National Cancer Institute's website,[42] a SEER-Medicare report,[43] and clinical expertise and collaborator input.

For women with lymphoma and gynecologic malignancies, receipt of radiation, field and dose were abstracted from KP EMR data if available, and otherwise from KP medical charts. Ovarian transposition (oophorexy) to reposition the ovaries outside of the field of radiation was also recorded from medical charts. In the North Carolina insurance claims, administration of radiation therapy was determined using HCPCS or CPT codes. These codes may identify the modality of radiation treatment, although some codes are non-specific (e.g. CPT 77401 "radiation treatment delivery"). Radiation field information was limited and dose was not included in the HCPCS/CPT codes. Similar to chemotherapy, included radiation codes were drawn from the Cancer Research Network[42] and consultation from clinical collaborators.

Gonadotropin-releasing hormone agonist (GnRHa) co-therapy (including goserelin, leuprolide, triptorelin, degarelix, histrelin, and nafarelin) may be used during chemotherapy as a means of ovarian suppression for fertility preservation.[5] Use of GnRHa was captured through using EHR data at KPNC and KPSC and cancer treatment insurance claims in North Carolina within 12 months of diagnosis.

Fertility Preservation and Assisted Reproductive Technology (ART) use

During the study diagnosis years, North Carolina and California did not mandate coverage for fertility preservation (initiated between cancer diagnosis and potentially gonadotoxic treatment), or coverage for IVF, though fertility preservation services for women at risk of iatrogenic infertility are now covered in California as of 2019.[23] Fertility and ART procedures after cancer treatment not covered by insurance can be challenging to identify in medical records or administrative claims if they are paid for out of pocket or received out of plan. The Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) database has covered more than 90% of all ART procedures performed in the

United States since 2004.[45] Reporting to SART CORS is required by its member clinics which must meet strict quality and safety metrics and requirements. The Centers for Disease Control and Prevention is mandated by the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493) to collect and report ART outcomes, and to solicit guidance from experts such as SART.[46] SART submits data to the CDC for its member clinics.

Women who undergo ART at SART member clinics, including Kaiser Permanente and UNC infertility clinics, provide consent for their data to be used for research. Roughly 10% of clinics are audited each year by SART and CDC for data validation, with low discrepancy rates (<4%) observed between medical records and data reported to the CDC for most data fields.[47] A third-party honest broker, Redshift Technologies, Inc. (Redshift), maintains the SART CORS database and facilitates linkage with individual-level data at KPNC, KPSC, and in North Carolina to ensure that identifiers are removed and coded, analytic datasets are used to preserve patient confidentiality.

After executing institutional memoranda of understanding and signing confidentiality agreements with SART, Redshift provided a linkage file with select identifiers (first and last name, date of birth, zip code, social security number), but not ART details, along with a unique person ID. This linkage file was matched to the AYA cancer sample and all comparison groups described previously. At the KP healthcare systems, the linkage was completed using MatchPro software; in North Carolina, LinkPlus software was use. Matching IDs were returned to Redshift, which then provided the ART information. These data, once received, were merged with limited datasets containing cancer diagnosis and cancer treatment information.

ART variables include, but are not limited to, age, race, medical history, medications (e.g. aromatase inhibitors, GnRH agonists and antagonists), parity, reasons for ART (e.g. diminished ovarian reserve, tubal disease, male infertility, etc.), autologous vs. donor oocytes, transfer of fresh or thawed oocytes/embryos, use of gestational carriers, reasons for cancellation (including illness and financial reasons), complications, embryo quality, and pre-implantation genetic testing. Embryo or oocyte cryopreservation was classified as fertility preservation if the oocyte retrieval dates fall between cancer diagnosis and first potentially gonadotoxic cancer treatment date (e.g. pelvic surgery, chemotherapy). Embryo cryopreservation is expected to be more commonly used than oocyte cryopreservation because oocyte cryopreservation was considered experimental until 2012.[48] The wide range of diagnosis years (2004–2016) will provide an opportunity to evaluate potential change in fertility preservation use and procedures over time.

Data sources for pregnancy and birth outcomes

At KPNC and KPSC, pregnancy databases and birth registries include not only livebirths, but also spontaneous abortion, termination, and other pregnancy outcomes. These registries are estimated to capture 99% of enrollee deliveries.[49] Additional pregnancy complications are identified using EHR data and ICD-9 and ICD-10 codes, including preeclampsia/eclampsia, gestational hypertension, gestational diabetes, and premature rupture of membranes as potential contributing factors to preterm birth by clinical presentation. In the

KP health system, the median rate of outpatient visits to any type of provider is similar between AYA cancer survivors and the non-cancer comparator group (3.5/person-year, interquartile range, IQR: 1.5–6.9; and 2.2/person-year, IQR: 0.7–4.6, respectively), providing evidence of ongoing medical surveillance and our ability to use routinely-collected clinical data to identify pregnancy and birth outcomes.[50]

In North Carolina, livebirths are identified by linkage of the Central Cancer Registry with statewide vital records using a probabilistic algorithm that incorporates maternal name, date of birth, social security number, and maiden name at the North Carolina State Center for Health Statistics. From birth certificates, information is available on infant birth weight, gestational age, race/ethnicity, maternal parity, smoking during pregnancy, vaginal or cesarean delivery, previous deliveries (including preterm or small-for-gestational age deliveries), education, prenatal care, plural birth, marital status, pregnancy-associated hypertension, and premature rupture of membranes in all study years for both women with and without a cancer history. Study participant records are also linked with national maternal and statewide fetal death files, and the North Carolina Birth Defects registry, as many birth defects are not identified at birth but during pediatric care in the months that follow. North Carolina participates in the CDC-funded Centers for Birth Defects Research and Prevention to conduct active population-based surveillance using standard case definitions from the National Birth Defects Prevention Study and National Birth Defects Prevention Network.

Comparison groups

To assess risk of clinical pregnancy and pregnancy loss among AYA women with cancer, a comparison cohort of women without a prior cancer diagnosis was identified in California using KPNC/KPSC electronic health records (EHRs), cancer registries, mortality files, and membership databases. Women without cancer were matched individually 5:1 to AYA cancer survivors on age, health plan enrollment year, and medical facility/service area. To be eligible for matching, women without cancer were required to be ages 15–39 years, cancer-free, and enrolled in the KPNC or KPSC health plan at the index date (the date of diagnosis for matched AYA cancer survivors), and have six-months continuous enrollment in the KPNC/KPSC health plans prior to the index date (allowing 90-day gaps in insurance coverage).

Sterilization procedures, either as part of cancer therapy (e.g. bilateral oophorectomy for ovarian cancer), or for other indications (e.g. tubal ligation, hysterectomy for benign conditions), are recorded and dated for both women with (all study sites) and without (KP only) cancer using procedure codes from the health system (KP) or insurance claims (North Carolina). This information will be used to describe both groups, and to inform the appropriate risk sets and censoring dates for analyses that examine time from diagnosis (or corresponding index date for women without cancer) to pregnancy. While expected to be rare, it will also allow for the possibility for fertility preservation strategies to be used prior to cancer-related surgery and subsequent births to occur through the use of a gestational carrier, as recorded in the SART database.

At all three study sites, a sample of births to mothers without a cancer history was identified for comparison of adverse birth outcomes between births to women with cancer and those

without. Births to mothers without a cancer history were matched 5:1 to births that occurred after a cancer diagnosis. Births were identified from KPNC/KPSC birth registries and North Carolina statewide birth certificate files. Births at KPNC/KPSC were matched on calendar year of birth, maternal age at birth, and enrollment start year. Births in North Carolina were matched on month and year of delivery, and maternal age at birth. Race/ethnicity was not a matching factor but is collected across all samples for future analyses that consider the role of race/ethnicity in overall associations or stratify on these characteristics.

Survey data

The AYA Horizon Study online survey was developed with ancillary funding from the UNC Lineberger Comprehensive Cancer Center to query receipt of fertility counseling, attempts to conceive, and self-reported cancer recurrence. These characteristics are not uniformly available in existing state cancer registries or health system databases and complement the parent study's pregnancy-focused aims. The developmental award supported two postal mailings (an introductory and reminder letter) at all three study sites to invite women to complete an online Qualtrics survey in English. Eligibility criteria included diagnosis in 2004–2016 to span the time period when data linkage was performed with public and private insurance claims in North Carolina and with the SART CORS database across study sites. Women who were alive and ages 18 years and older at the time of contact (September 2018-November 2019), and in California, were required to be current enrollees in the KPNC or KPSC health plans.

We adapted a survey that was previously developed to capture reproductive intentions and fertility-related experiences in cancer populations.[51] The survey was modified to be appropriate for survivors across cancer types in consultation with collaborating oncologists who specialize in breast, lymphoma, and gynecologic oncology. Additional priority content areas were solicited to expand the focus of the AYA Horizon Study to include other central concerns of AYAs, including genetic testing, clinical trial enrollment, health behaviors, financial concerns, caregiving roles, advance care planning, and technology preferences for information needs. Some modifications were made by each study site to reflect IRB-specific language preferences, or to minimize redundancies (e.g. with data available through the health plans, etc.).

To ensure the survey's acceptability and understanding by AYAs with cancer, we conducted one-hour cognitive interviews with nine AYA cancer survivors in North Carolina by phone (UNC IRB#17–2858). Participants were female, ages 20–39 at cancer diagnosis, had been diagnosed with cancer 3–9 years previously (ages 24–48 at interview), and spanned multiple cancer types (3 thyroid, 3 breast, 2 melanoma, 1 gynecologic). Women were sent a link to complete the online survey on their own, followed by a recorded, structured phone interview that queried general feedback and specific understanding of questionnaire items. In appreciation for their time, participants received a $20 Amazon gift card for pre-testing the survey.

The final survey draft and protocol were approved by the IRBs at UNC, KPNC, and KPSC, and the protocol was approved by the North Carolina State Center for Health Statistics Director and the Advisory Committee on Cancer Coordination and Control. All participants

provided informed consent within the online survey. The North Carolina mailing was conducted by the UNC Odum Institute for Social Science Research; the KPNC/KPSC mailings were sent by the health systems. At all three sites, returned mailings due to incorrect address information were tracked. Based on available resources, and to enhance participation and the potential for future contact, respondents were given the option to participate in a drawing based on chance for one of forty $50 Amazon gift cards where allowed by the IRB.

At KPNC and KPSC, 258 of 3,500 (7.4%) and 41 of 2,321 (1.8%) mailings, respectively, were returned as non-deliverable. At KPNC, letters were more likely to be returned as non-deliverable for women diagnosed in earlier calendar years (e.g., 10.9% returned for 2004 vs. 2.8% returned for 2016; $p<0.0001$) and were less likely to be returned for Asian women (i.e. 11.6% returned for Black women, 8.7% for White, and 4.1% for Asian; $p<0.001$) and women who received chemotherapy (e.g. 8.8% returned for surgery only vs. 5.5% returned for any chemotherapy; $p<0.001$). The proportion of returned letters did not substantively differ by age at diagnosis, Hispanic ethnicity, or stage. Analysis of returned mail was not available for KPSC, though the proportion of returned letters was low overall (1.8%).

In North Carolina, 10,077 addresses were available from the Central Cancer Registry for AYAs who met study eligibility criteria and were run through National Change of Address database for address updates prior to the first mailing. Of these, 2,445 letters (24.3%) were returned as non-deliverable. Returned letters were more common for women who were younger at diagnosis (e.g., 29.3% returned for ages 18–24 vs. 20.3% returned for ages 35–39 years; $p<0.0001$); diagnosed in earlier years (e.g., 30.1% returned for 2004 vs. 11.6% returned for 2015; $p<0.0001$); Black women (e.g., 31.0% returned for Black vs. 22.7% for White; $p<0.0001$) and Hispanic women (28.5% returned for Hispanic vs. 24.0% returned for non-Hispanic women; $p=0.01$).

Among the mailed letters that were not returned across the three study sites, 8 women were deceased and 14 were ineligible due to cancer type or diagnosis age. Cancer registry/EHR characteristics for survey respondents and the invited sample across study sites are shown in Table 3; the overall participation proportion was 12.8% (10.4–16.4% across study sites). Survey participation reflected the invited sample for age at diagnosis, but response varied by cancer type, race, Hispanic ethnicity, SEER summary stage, and cancer treatment (all $p<0.0001$) (Table 3). Women with lower survey response included: those with gynecologic cancer (8.8% for those with gynecologic cancer vs. 10.5%−12.7% for all other cancer types; all $p<0.04$); Black and Asian women (5.6% for Black and 7.7% for Asian vs. 12.8% for White; $p<0.0001$); Hispanic women (9.6% for Hispanic vs. 11.7% for non-Hispanic; $p=0.005$); and women who received surgery alone (10.2% for those who received surgery alone vs. 12.8% for those who received any chemotherapy; $p<0.0001$). The low overall response was likely due, in part, to the long diagnosis window (up to 15 years previous), use of only 2 postal invitations and single survey modality (online in English) protocol, based on available resources. In a recent multi-modal (mail and phone recruitment; paper, web and phone survey options) U.S.-based survey of AYA cancer survivors diagnosed within the previous 14 months, survey response was 43% (N=332 male and 192 female respondents); the relatively higher response rate can likely be attributed to the more recent diagnoses, more

intensive follow-up procedures (e.g., repeated mailings and telephone calls for non-respondents) and an incentive of $25 for survey completion and an additional $25 for completing medical record release forms.[52] Despite the suboptimal overall response in our study, information reported directly from >1,600 female participants, with a well-defined sampling frame, provides a valuable resource for understanding the experiences of women diagnosed with AYA cancers.

Discussion

Opportunities and challenges

The overarching goal of the AYA Horizon Study is to examine clinical pregnancy outcomes after diagnosis of the most common AYA cancers in women. It is a cohort identified from existing state and integrated health care records, and followed passively for fertility preservation and other ART procedures, as well as pregnancy and birth outcomes. Passive data collection through linkage reduces participant burden and prevents systematic cohort attrition or potential selection biases that can occur with active participation requirements.[53] Use of existing data also provides efficiency in cost and time relative to *de novo* data collection.[53] To this structure, we have added information from a subset of women who have administrative insurance claims in North Carolina and from a subset who responded to an online survey to collect information on experiences that are not routinely captured in existing health data. This combination of data sources allows us to compare information and data quality across sources; for example, to compare cancer treatment information from a state cancer registry to administrative insurance claims,[54] or assess similarities and differences between survey responders to the invited sample.

Use of existing data that does not require active research participation can also help to address concerns regarding generalizability when active participation varies between groups. Our existing data sources include a sample of female AYA cancer survivors that includes >1,200 African American women, >1,400 Asian women, >1,600 Medicaid enrollees, and >2,500 Hispanic women. This sample will be key to document the use of fertility preservation between these groups, and subsequent pregnancy outcomes. In our survey sample, we observed that active response was low overall, and notably lower among minority groups compared to non-Hispanic white women. The potential impact of differential response can be considered in future sensitivity analyses using this data, and will inform the allocation of resources in future studies to reach minority women.

Based on the included data sources, we will not directly address cancer recurrence. Censoring at 6-months prior to cancer recurrence did not influence birth rates in a prior study.[10] While KPNC and KPSC have disenrollment dates to censor follow-up, we cannot account for women who move out of North Carolina between cancer diagnosis and pregnancy or delivery. However, in U.S. census data for North Carolina in 2000–2010, only 6–7% of all women moved out-of-state, with residents ages 25–29 twice as likely to move out of state.[55] With this information, we estimate that 15% of AYA women may have moved out-of-state during the study period. Therefore, the population stability remains high at an estimated 85% over 10 years.

Research priorities and future directions

An estimated 60% of AYA women with a cancer diagnosis want the possibility of children after treatment.[56] Having biological children is an important option for parenthood because a prior cancer diagnosis may violate medical screening requirements in adoption.[57] Accepted fertility preservation strategies, such as embryo/oocyte cryopreservation, also have potential to exacerbate existing racial and economic disparities in cancer care and outcomes, given that embryo/oocyte cryopreservation can be expensive and is rarely covered by insurance. Even in states with mandated infertility coverage, AYA cancer patients may not qualify for coverage at the time services are needed because they are not infertile prior to cancer treatment.[44] Based on these barriers to fertility preservation, the majority of births to AYA cancer survivors are likely to be naturally conceived. In our prior research in North Carolina, we observed a 15% cumulative incidence of livebirth after AYA cancer over 10 years.[58] The Horizon study will newly contribute high quality data from California, detailed cancer treatment information, and the contribution of fertility preservation (including potential use of donor gametes or gestational carriers) to subsequent birth rates across study sites.

High-quality evidence on the clinical outcomes of future pregnancies is crucial information for AYA cancer survivors in treatment and prenatal planning. Studies of AYA cancer survivors abroad and of U.S. childhood cancer survivors report increases in infertility, miscarriage risk, delivery complications, and adverse birth outcomes.[10–18,59,60] The impact of these risks may be magnified for AYA cancer survivors in the U.S. compared to European or other settings due to the higher prevalence of adverse birth outcomes in the U.S. overall, especially among minority and low-income groups.[26,29] Studies of pregnancy risks among adult survivors of childhood cancers reflect a longer interval between cancer treatment and pregnancy compared to women diagnosed with AYA cancers, and may not include the use of accepted fertility preservation options that are available only after puberty.

The AYA Horizon study will provide contemporary evidence on pregnancy risks among female survivors of the most common AYA cancer types that can be directly applied to fertility preservation, preconception, and prenatal counseling during cancer care and survivorship. This evidence base may be used by the oncology team and fertility specialists during active treatment planning; by fertility specialists who have patients who initiate ART years after cancer treatment; or by family medicine or obstetrics and gynecology providers when women conceive after an AYA cancer diagnosis, and will inform patient-provider dialogue around family planning.

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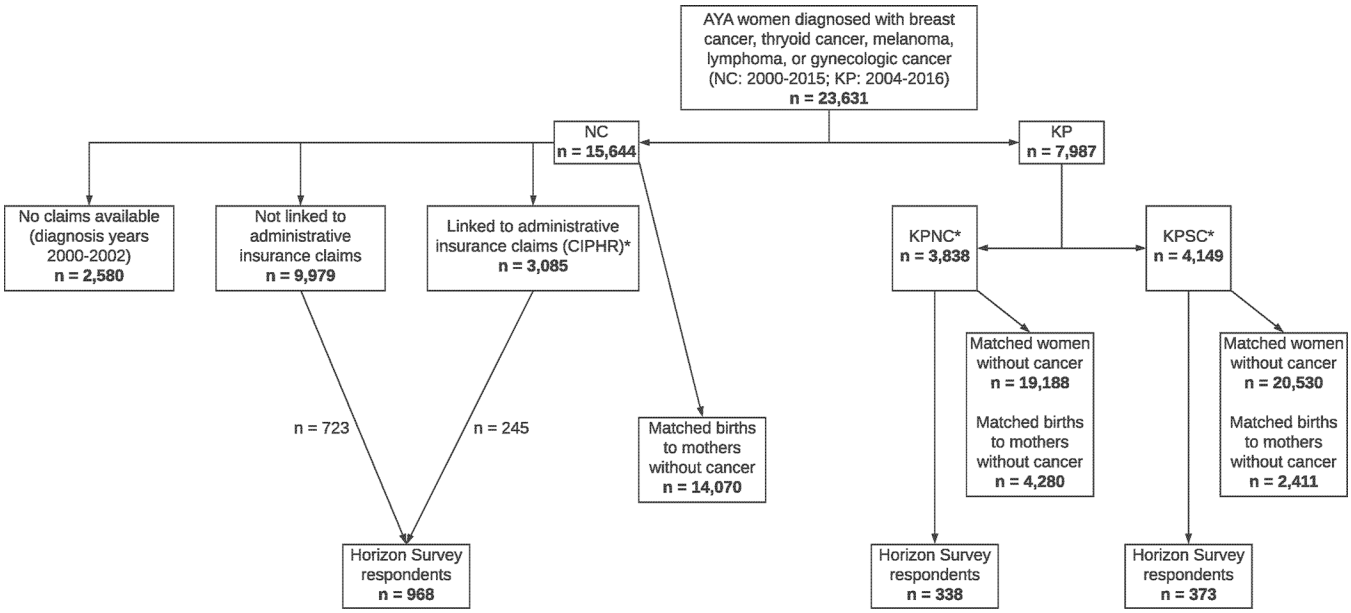

Figure 1.

Flow chart of study samples and data sources from the Horizon cohort, including existing, administrative data from 11,072 women with an AYA cancer diagnosis and 1,679 women who responded to the Horizon Study online survey. NC=North Carolina; KP=Kaiser Permanente; KPNC=Kaiser Permanente Northern California; KPSC=Kaiser Permanente Southern California; CIPHR=Cancer Information Population Health Resource. *Women who satisfied study site-specific pre- and post-diagnosis enrollment criteria.

Table 1.

AYA Horizon Study cohort characteristics using existing, health system or administrative insurance claims data

	UNC CIPHR		KPSC		KPNC		Total	
Total, N	3,085		4,149		3,838		11,072	
Diagnosis years	2003–2015		2004–2016		2004–2016			
Cancer type[1]								
Gynecologic	509	16.5%	748	18.0%	556	14.5%	1,813	16.4%
cervical	276	8.9%	320	7.7%	266	6.9%	862	7.8%
uterine	117	3.8%	269	6.5%	137	3.6%	523	4.7%
ovarian	116	3.8%	159	3.8%	153	4.0%	428	3.9%
Lymphoma	351	11.4%	435	10.5%	439	11.4%	1,225	11.1%
Hodgkin lymphoma	196	6.4%	223	5.4%	257	6.7%	676	6.1%
non-Hodgkin lymphoma	155	5.0%	212	5.1%	182	4.7%	549	5.0%
Melanoma	411	13.3%	445	10.7%	561	14.6%	1,417	12.8%
Thyroid	630	20.4%	1,178	28.4%	877	22.9%	2,685	24.3%
Breast	1,184	38.4%	1,343	32.4%	1,405	36.6%	3,932	35.5%
in situ	134	4.3%	129	3.1%	147	3.8%	410	3.7%
invasive	1,050	34.0%	1,214	29.3%	1,258	32.8%	3,522	31.8%
Age at diagnosis								
15–17	44	1.4%	86	2.1%	82	2.1%	212	1.9%
18–24	317	10.3%	444	10.7%	370	9.6%	1,131	10.2%
25–29	480	15.6%	592	14.3%	557	14.5%	1,629	14.7%
30–34	819	26.5%	1,135	27.4%	1,105	28.8%	3,059	27.6%
35–39	1,425	46.2%	1,892	45.6%	1,724	44.9%	5,041	45.5%
Hispanic ethnicity	94	3.0%	1,724	41.6%	759	19.8%	2,577	23.3%
Race								
White	2,283	74.0%	2,536	61.1%	2,215	57.7%	7,034	63.5%
African American	675	21.9%	355	8.6%	225	5.9%	1,255	11.3%
Asian	42	1.4%	537	12.9%	834	21.7%	1,413	12.8%
Other	36	1.2%	50	1.2%	550	14.3%	636	5.7%
Unknown	47	1.5%	671	16.2%	14	0.4%		

	UNC CIPHR		KPSC		KPNC		Total	
Any Medicaid/state-subsidized enrollment, %	1,320	42.8%	199	4.8%	160	4.2%	1,679	15.2%
Post-diagnosis continuous enrollment, %								
12 months[2]	1,603	95.5%	3,768	90.8%	3,358	87.5%	8,729	91.3%
Deaths[3]	8	0.5%	59	1.4%	38	1.0%		
60 months[2]	525	49.3%	1,877	62.7%	1,670	51.7%	4,072	54.6%
Deaths[3]	51	4.8%	190	6.3%	158	4.9%		

[1] All cancer is invasive except for breast cancer.

[2] For the UNC CIPHR Population, continuous enrollment calculations restricted to women with private insurance only (N=1,765). Of these, 1,679 women were eligible for 12 month continuous enrollment and 1,065 women were eligible for 60 months continuous enrollment based on diagnosis dates ≥12 and ≥60 months prior to the end of the private insurance claims window (2015). For the KPSC Population, the full sample of 4,149 women was eligible for 12 month enrollment, and 2,993 women were eligible for 60 month enrollment based on diagnosis dates. For the KPNC Population, the full sample of 3,838 women was eligible for the 12 month enrollment, and 3,229 women were eligible for 60 month enrollment based on diagnosis dates.

[3] For the UNC CIPHR Population, indicates deaths that occur within 12- or 60-months of cancer diagnosis during private insurance enrollment.

Table 2.

Characteristics of North Carolina cancer survivors in the AYA Horizon Study (who have CIPHR-linked insurance claims data) compared to AYA cancer survivors in North Carolina who do not have CIPHR-linked administrative insurance claims data.

	AYA cancer survivors with linked administrative insurance claims data		AYA cancer survivors without linked administrative insurance claims data	
	N	**%**	**N**	**%**
Total Cancer Cases	3,085	100.0%	9,979	100.0%
Cancer type[1]				
Gynecologic	509	16.5%	1,708	17.1%
Lymphoma	351	11.4%	912	9.1%
Melanoma	411	13.3%	1,541	15.4%
Thyroid	630	20.4%	2,264	22.7%
Breast	1,184	38.4%	3,554	35.6%
in situ	134	4.3%	360	3.6%
invasive	1,050	34.0%	3,194	32.0%
Age at diagnosis				
15–17	44	1.4%	143	1.4%
18–24	317	10.3%	955	9.6%
25–29	480	15.6%	1,580	15.8%
30–34	819	26.5%	2,695	27.0%
35–39	1,425	46.2%	4,606	46.2%
Hispanic ethnicity, %	94	3.0%	767	7.7%
Race, %				
White	2,283	74.0%	7,538	75.5%
African American	675	21.9%	1,820	18.2%
Asian	42	1.4%	230	2.3%
Other	36	1.2%	84	0.8%
Unknown	47	1.5%	291	2.9%
Stage				
In situ	128	4.1%	332	3.3%
Localized	1,594	51.7%	5,269	52.8%
Regional	902	29.2%	2,704	27.1%
Distant	239	7.7%	679	6.8%
Unstaged/unknown	56	1.8%	293	2.9%
Missing	166	5.4%	702	7.0%
Rural/Urban Residence[2]				
Urban	2,170	70.3%	7,453	74.7%
Rural	914	29.6%	2,512	25.2%
Missing	1	0.0%	14	0.1%

[1] All cancer is invasive except for breast cancer.

[2]Defined by USDA Rural-Urban Continuum Codes for residence at cancer diagnosis.

Table 3.

Characteristics of AYA Horizon Study survey participants and the invited samples[1] across study sites.

	Combined participants	Combined invited sample	North Carolina participants	North Carolina invited sample	KPSC participants	KPSC invited sample	KPNC participants	KPNC invited sample
Total, N	1,679	13,132	968	7,611	373	2,280	338	3,241
Years since diagnosis, %								
<3	3.0%	2.3%	0.0%	0.0%	13.4%	13.1%	0.0%	0.0%
3–5	36.9%	29.8%	39.6%	29.7%	34.9%	30.9%	31.7%	29.1%
6–9	32.4%	32.7%	33.0%	33.7%	30.8%	30.3%	32.5%	31.9%
10–15	27.7%	35.3%	27.5%	36.6%	20.9%	25.7%	35.8%	39.0%
Age at diagnosis, %								
15–17	1.1%	0.9%	0.0%	0.0%	3.2%	1.8%	2.1%	2.2%
18–24	9.8%	8.9%	9.5%	9.1%	10.5%	7.1%	9.8%	9.8%
25–29	15.6%	14.6%	15.1%	15.3%	14.7%	12.6%	18.0%	14.4%
30–34	26.5%	27.6%	26.4%	26.8%	28.4%	28.1%	24.6%	29.0%
35–39	47.0%	48.1%	49.0%	48.9%	43.2%	50.3%	45.6%	44.6%
Cancer type[2], %								
Gynecologic	11.3%	14.9%	10.7%	15.0%	14.2%	16.0%	9.5%	14.0%
Cervical	5.6%	7.3%	5.3%	7.8%	6.4%	6.2%	5.6%	6.8%
Uterine	3.6%	4.6%	3.5%	4.5%	5.4%	6.4%	1.8%	3.7%
Ovarian	2.1%	3.0%	2.0%	2.7%	2.4%	3.3%	2.1%	3.5%
Lymphoma	10.9%	9.6%	10.1%	8.8%	10.2%	9.8%	13.9%	11.3%
Hodgkin lymphoma	6.9%	5.5%	6.3%	4.9%	4.8%	5.2%	10.9%	6.9%
Non-Hodgkin lymphoma	3.7%	4.1%	3.8%	3.8%	4.0%	4.6%	3.0%	4.4%
Melanoma	14.4%	14.6%	14.3%	16.0%	12.9%	9.5%	16.6%	14.9%
Thyroid	23.5%	25.7%	22.9%	25.2%	26.8%	30.0%	21.6%	24.0%
Breast	39.9%	35.2%	41.9%	35.1%	35.9%	34.6%	38.5%	35.7%
in situ	4.3%	4.4%	4.9%	4.6%	3.2%	3.8%	4.1%	4.1%
invasive	33.9%	30.5%	36.8%	29.9%	26.0%	30.8%	34.3%	31.6%
Age at survey, %								
18–24	2.3%	1.4%	1.1%	0.7%	5.6%	3.1%	2.1%	1.7%

	Combined participants	Combined invited sample	North Carolina participants	North Carolina invited sample	KPSC participants	KPSC invited sample	KPNC participants	KPNC invited sample
25–29	5.2%	4.5%	5.5%	4.3%	5.1%	4.3%	4.4%	5.0%
30–34	13.1%	10.9%	12.4%	11.1%	14.5%	10.2%	13.6%	11.0%
35–39	23.1%	21.1%	22.6%	20.4%	24.4%	22.2%	23.1%	21.9%
40–44	31.4%	31.5%	33.1%	31.9%	29.8%	32.4%	28.7%	30.0%
45–49	19.2%	23.4%	20.2%	24.6%	15.8%	21.7%	20.1%	21.7%
50–53	5.5%	7.0%	5.1%	7.0%	4.8%	5.7%	7.7%	8.0%
54+	0.1%	0.2%	0.0%	0.0%	0.0%	0.4%	0.3%	0.6%
Race[3]								
White	81.1%	70.4%	89.4%	78.7%	70.2%	60.7%	69.2%	57.7%
African American	5.5%	11.9%	7.5%	16.0%	3.5%	8.2%	2.1%	4.9%
Asian	6.0%	9.2%	2.1%	2.2%	8.0%	13.9%	15.1%	22.5%
Other	4.9%	4.4%	0.9%	1.0%	7.5%	1.3%	13.6%	14.5%
Missing	2.4%	4.1%	0.1%	2.2%	10.7%	15.9%	0.0%	0.4%
Hispanic ethnicity[3]	13.2%	15.9%	3.2%	5.6%	38.3%	43.6%	14.2%	20.4%
SEER Summary stage								
In situ	4.3%	4.4%	4.9%	4.7%	3.2%	3.8%	4.1%	4.1%
Local	51.3%	59.5%	54.3%	60.4%	44.0%	59.0%	50.9%	57.7%
Regional	33.7%	29.3%	34.8%	27.6%	26.5%	31.5%	38.5%	31.9%
Distant	4.8%	5.0%	4.8%	5.0%	4.3%	4.9%	5.3%	5.2%
Unstaged	0.9%	1.6%	1.2%	2.2%	0.0%	0.0%	0.9%	1.1%
Missing[4]	4.9%	0.2%	0.0%	0.1%	22.0%	0.7%	0.3%	0.0%
Cancer treatment[3]								
Surgery only	37.1%	41.9%	37.4%	43.2%	35.7%	38.7%	37.9%	41.0%
Radiation, no chemotherapy	19.0%	18.2%	18.7%	17.5%	22.0%	20.8%	16.6%	18.2%
Any chemotherapy	41.9%	36.5%	42.0%	35.8%	39.1%	37.7%	44.4%	37.5%
No surgery, radiation, or chemotherapy	2.0%	3.0%	1.9%	3.1%	2.9%	2.8%	1.2%	3.0%
Missing	0.1%	0.4%	0.0%	0.5%	0.3%	0.0%	0.0%	0.3%

[1] Excludes returned mail (NC: 2,445; KPSC: 41; KPNC: 258) and ineligible participants (NC: 21; KPNC: 1)

[2] All cancer is invasive except for breast cancer.

[3] Data obtained from self-reported survey responses for the following number of women: race (NC: 14; KPSC: 85; KPNC: 1), ethnicity (KPSC: 74; KPNC: 73), and cancer treatment (NC: 6; KPSC: 79; KPNC: 62)

[4] Missingness may be higher among survey participants compared to the invited sample because consent to link one's survey response to external data (e.g., electronic health record) was not available for all survey participants.